

REMARKS

The present application is directed to compositions containing novel polycationic carbohydrates. In particular, the present application is directed to novel polycationic compounds wherein the polycationic carbohydrate is a water-soluble alkylated chitosan, or a salt thereof. In addition, methods for the use of the above polycationic carbohydrates as immunostimulants are disclosed. Claims 1, 3-6, 11-22, and 36-37 are pending. Claims 2, 7-10, 23-35 and 38-39 are cancelled without prejudice. Claims 1, 3, 6, 16, and 21 are currently amended. Support for the following remarks is found throughout the specification, and no new matter is introduced. In light of the following remarks, favorable consideration of the present application is respectfully requested.

Claim rejections under 35 U.S.C. §102(b)

In the Final Office Action mailed May 12, 2005, the Examiner rejected Claims 1-2, 4-6, 11-12, 16 and 18-19 under 37 U.S.C. §102(b), as being anticipated by Illum (WO 97/20576) (hereinafter "Illum"). Applicants respectfully submit that the amendments to the claims overcome the rejection.

The Examiner's rejection is based on a broad interpretation of the term "a polycationic carbohydrate, which is a water-soluble alkylated chitosan or a pharmaceutically acceptable salt or derivative thereof". The Examiner asserts that, because of the presence of the word "derivative", the term covers any chitosan derivative such as those disclosed by Illum. Applicants respectfully submit that the phrase "derivative thereof" covers only derivatives that are polycationic carbohydrates and alkylated chitosans, neither of which are disclosed in Illum. However, in order to facilitate prosecution, this term has been removed from the amended claims.

Applicants respectfully submit the amended claims are not anticipated by Illum because Illum does not disclose a polycationic chitosan, an alkylated chitosan, a trimethyl chitosan (TMC), nor an N-carboxymethyl chitosan.

In the Office Action mailed May 5, 2005 the Examiner stated that Illum teaches a polycationic carbohydrate that is a water-soluble alkylated chitosan (page 5, lines 20 to 24 and lines 25 to 28). In the fourth paragraph of Section 5 of the Office Action mailed May 5, 2005, the Examiner stated, Illum teaches that "chitosan derivatives include esters, ethers or other derivatives formed by bonding acyl and/or alkyl groups." Applicants respectfully disagree. There is no teaching of the alkylation of chitosan in Illum, and the chitosans disclosed therein are not alkylated. Illum explains at page 5, lines 20 to 24, that chitosan is made by the deacetylation of chitin by hydrolysis. Chitin is a polysaccharide, i.e. a carbohydrate, which is formed from N-acetyl glucosamine units. The deacetylation transforms a proportion of the -HNCCH_3 groups of chitin into the -NH_2 groups of chitosan. As the degree of deacetylation can be varied, a variety of chitosans are produced, in which the proportion of -HNCCH_3 to -NH_2 groups is varied. Illum mentions the degree of deacetylation of the parent chitin that they prefer in the chitosan to be used, but otherwise is silent with regard to the nature of the chitosan. Moreover, chitin and chitosans are not polycationic carbohydrates as the -HNCCH_3 and -NH_2 groups do not carry a positive charge. Chitosan glutamate is commercially available and is specified and used in Illum. In chitosan glutamate some of the -NH_2 groups of the chitosan are formed into a $\text{-HNCCH(NH}_2\text{)CH}_2\text{CH}_2\text{CO}_2\text{H}$ group. This group does not carry a positive charge and therefore chitosan glutamate is not a polycationic carbohydrate.

Applicants respectfully submit the present inventors have taken chitosans and chemically modified the -NH_2 groups by organically bonding one or more alkyl group to the N atom to provide the N atom with a positive charge **and** to form polycationic carbohydrates which are alkylated chitosans. There is no teaching or suggestion of the chemical modification of chitosans in Illum and thus there is no teaching or suggestion of the alkylation of chitosans therein.

The applicants of the present application found that compounds, in which a proportion of the N atoms are trimethylated to give $\text{-N(CH}_3\text{)}_3^+$ groups or are bonded to the substituted alkyl group carboxymethyl to give $\text{-NH}_2\text{CH}_2\text{CO}_2\text{H}^+$, have remarkable immunostimulatory properties. The use of two specific polycationic, alkylated chitosans as

immunostimulants is claimed herein. Applicants respectfully submit this use is not anticipated by Illum.

In the forth paragraph of Section 5 of the Office Action mailed May 5, 2005, the Examiner states, with reference to Illum, “disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or non-preferred embodiments” and cites *In re Susi*. Based on this logic, Illum’s disclosure is not limited to the commercially available chitosan glutamate that is used in their examples and is their preferred chitosan. Applicants concur that Illum’s sole use of the specific chitosan does not teach away from the broader and non-preferred disclosure of Illum. However, the broader disclosure (as demonstrated and reasoned above) does not include polycationic, alkylated chitosans nor the two specifically claimed chitosans of the present application.

The Examiner also cites *In re Gurley*, which states that “a known or obvious composition does not become patentable just because it is taught as being inferior to some other product for the same use”. Applicants concur with the Examiner. Illum is relevant for all it discloses. Applicants submit that, if the two presently claimed chitosans were known or obvious from Illum and Illum taught that they were inferior to other disclosed compounds, those chitosans would not become new or non-obvious because they were taught as being inferior. This is, however, not the case here. The two claimed chitosans are not taught or suggested by Illum, and Illum does not teach that they are inferior.

The Examiner also cites *In re Casey* and *In re Otto* to support the argument that if a prior art structure is capable of performing an intended use it anticipates a claim to the use of that structure for that use and that to be patentable a claimed invention must include a structural difference to distinguish it from the prior art. As stated above, the two specifically claimed chitosans are not taught in the prior art disclosure of Illum. Furthermore, the two specifically claimed chitosans are structurally different from the chitosans of Illum in that they are polycationic and alkylated.

Applicants respectfully submit that the claims as presented herein are directed to the use of two specified chitosans as immunostimulants and to compositions containing them.

These compositions include particle compositions wherein the chitosans are distributed throughout the particle and compositions containing pluronic particles coated with the chitosans.

Applicants respectfully submit that the claims presented herein specify that the two specific chitosans are trimethyl chitosan (TMC) and N-carboxymethyl chitosan. Prior to the teachings of the present application, it was not known that these compounds were immunostimulants and their use as such, and the use of immunostimulant compositions containing them, are both novel and non-obvious. Accordingly, applicants submit they have overcome the Examiner's rejection under 35 U.S.C. §102(b) and request its withdrawal.

Claim rejections under 35 U.S.C. §103(a)

In the Final Office Action mailed May 12, 2005, the Examiner rejected Claims 13-15, 17 and 20-22 under 35 U.S.C. §103(a), as being unpatentable over Illum (WO 97/20576) (discussed above) in view of Eyles et al., (hereinafter "Eyles"). Applicants respectfully traverse.

As explained above, Illum fail to teach or suggest a pharmaceutical composition comprising a polycationic carbohydrate, wherein the polycationic carbohydrate is a water-soluble alkylated chitosan selected from the group consisting of trimethyl chitosan and N-carboxymethyl chitosan or a salt thereof.

In addition, all of the above rejected claims (Claims 13-15, 17 and 20-22) are dependent on presently amended Claim 1 or Claim 6, which are, in turn, dependent on amended Claim 1. As discussed above applicants respectfully submit that the compositions of the instant application are novel and non-obvious over the teachings of Illum. Furthermore, the deficiencies of Illum are not satisfied by Eyles for at least the following reasons. Eyles does not disclose, suggest or motivate one of ordinary skill in the art to use the two specified chitosans as immunostimulants. Accordingly, applicants submit they have overcome the Examiner's rejection under 35 U.S.C. §103(a) and request its withdrawal.

In the Final Office Action mailed May 12, 2005, the Examiner rejected Claim 3 under 35 U.S.C. §103(a), as being unpatentable over Illum (WO 97/20576) (discussed above) in view of Kotze et al., (hereinafter "Kotze"). Applicants respectfully traverse.

As explained above, Illum fail to teach or suggest a pharmaceutical composition comprising a polycationic carbohydrate, wherein the polycationic carbohydrate is a water-soluble alkylated chitosan selected from the group consisting of trimethyl chitosan and N-carboxymethyl chitosan or a salt thereof.

In addition, Claim 3 depends directly from amended Claim 1. As discussed above, applicants respectfully submit that the compositions of the instant application are novel and non-obvious over the teachings of Illum. Furthermore, the deficiencies of Illum are not satisfied by Kotze for at least the following reasons.

In the first paragraph of Section 7 of the Office Action mailed May 12, 2005, the Examiner states that it would be obvious to use “the known polycationic carbohydrates as taught by Illum and modify the compositions to include the N-trimethyl chitosan as taught by Koetze *et al.* Applicants respectfully submit, as discussed above, that Illum fails to teach polycationic carbohydrates.

In the second paragraph of section 7, with regard to applicants’ previously submitted argument, the Examiner’s position is stated to be that disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or non-preferred embodiments and cites *In re Susi*. Applicants concur with the Examiner. Illum’s disclosure is not limited to the commercially available chitosan glutamate that is used in their examples and is their preferred chitosan. Applicants submit that Illum’s sole use of chitosan glutamate does not teach away from the broader and non-preferred disclosure of Illum. However, the broader disclosure (as demonstrated and reasoned above) does not include polycationic, alkylated chitosans, nor the two specifically claimed chitosans of the present application.

The Examiner also states, “a known or obvious composition does not become patentable just because it is taught as being inferior to some other product for the same use.” If the two presently claimed chitosans were known or obvious from Illum, they would remain known and obvious even if Illum taught that they were inferior to other disclosed compounds. This is not, however, the case here. The two specifically claimed chitosans of the present application are not known or obvious from Illum, and Illum does not teach that they are inferior to their disclosed chitosans as immunostimulants. Similarly if the two presently claimed

chitosans were known or obvious from Koetze they would remain known and obvious even if Koetze taught that they were inferior for their purposes in comparison to other disclosed compounds, and a claim to those chitosans *per se* would not be patentable. The present applicants, however, are not claiming the two chitosans *per se*, but a specific use of those chitosans.

In the third paragraph of Section 7 of the Office Action mailed May 12, 2005, with regard to applicants' previously submitted argument, the Examiner argues that the present claims "do not become patentable simply because they have been described as somewhat inferior to some other product for the same use." Applicants respectfully submit that Koetze does not describe that TMC is inferior for the presently claimed use. Koetze is only concerned with the use of TMC as an absorption enhancer, i.e. as a transport provider, for certain drugs. Koetze merely teaches the use of TMC as an absorption enhancer, i.e. a simple transport device, across intestinal cells. For this use, Koetze concludes that TMC is as effective as chitosan hydrochloride and chitosan glutamate. Koetze is silent as to the use of TMC as an immunostimulant.

Applicants respectfully submit that the claimed use of trimethyl chitosan (TMC) and N-carboxymethyl chitosan as immunostimulants is non-obvious in view of both Koetze and Illum. Accordingly, applicants respectfully request withdrawal of the 35 U.S.C. §103(a), second paragraph, rejection.

The Examiner's further argument in the third paragraph of section 7 of the Office Action mailed May 12, 2005 with regard to inherency is not considered relevant as applicants are not claiming inherent subject matter or an inherent fact. Applicants submit they are not claiming an inherent property of a chitosan, but a novel use of two specific chitosans.

Applicants' previously filed arguments that the two specifically claimed chitosans exhibit an increased adjuvant effect, i.e. are particularly effective immunostimulants, and that TMC is known to be only as effective as chitosan hydrochloride and chitosan glutamate as an absorption enhancer were submitted to demonstrate that inventive input was required in determining that the two specified chitosans have a use as immunostimulants. The reasoning for this such argument is as follows. Illum discloses that chitosans have immunostimulant

properties. If chitosans were a homogenous group, the members of which all shared the same properties and all to the same degree, then from the disclosure of Illum a skilled person could predict that all chitosans were immunostimulants and a claim to the use of any particular chitosan would not be patentable. In contrast, if the group were not homogenous and there were specific subgroups or compounds within the overall group that differed, prediction would not be possible and the skilled person would need to use his ingenuity to select from the vast number of possible chitosans individual subgroups or compounds to test and look at on its own merit. The fact that the two specifically claimed chitosans have been found to exhibit an increased adjuvant effect compared to other chitosans is evidence that chitosans do not form a homogeneous and thereby predictable group. The fact that TMC is only as effective as chitosan hydrochloride and chitosan glutamate when used as an absorption enhancer is evidence that variations between members of the group are not the same for any given use. Hence, a disclosure that a particular chitosan has one specific use cannot be used to predict or suggest with a reasonable expectation of success, that it will also have another use. In order to see whether a particular chemical modification produces a chitosan that has immunostimulatory properties it is necessary to make the chemical modification, i.e. to manufacture the modified compound and to test it. It would not be obvious for one of ordinary skill in the art to select TMC and N-carboxymethyl chitosan from all possible chitosans in order to establish their immunostimulatory effect without the exercise of inventive skills.

Accordingly, applicants respectfully submit that Illum and Kotze fail to provide a *prima facie* obviousness rejection because neither Illum or Kotze teach or suggest the compositions or methods as instantly claimed. Applicants respectfully submit they have overcome the Examiner's rejection under 35 U.S.C. §103(a) and request its withdrawal.

In the Final Office Action mailed May 12, 2005, the Examiner rejected Claims 22, 36 and 38 under 35 U.S.C. §103(a), as being unpatentable over Illum (WO 97/20576) (discussed above) and Eyles (discussed above) in view of Kotze et al., (discussed above).

Applicants respectfully traverse. Applicants respectfully submit that Claim 22 is dependent on newly amended Claim 1 and Claim 36 is dependent on Claim 6, which is in turn

dependent on amended Claim 1. As discussed above, the subject matter of Claim 1 has been demonstrated to be novel and non-obvious in relation to Illum, Eyles and Koetze. Accordingly, applicants respectfully submit they have overcome the Examiner's rejection under 35 U.S.C. §103(a) and request its withdrawal.

In addition, with respect to Claim 22, applicants reiterate that none of the prior art references teach cationic pluronics. The term pluronics is one used in the industry for block copolymers based on ethylene oxide and propylene oxide. Cationic pluronics include cations or have been bound to cationic moieties, see page 11, lines 20 to 23, and page 12, lines 26 to 31, of the present application. Poly-DL-lactide (PLA) is a polymer of lactic acid ($\text{CH}_3\text{CHOHCO}_2\text{H}$). It is not a block copolymer, it is not based on ethylene oxide and propylene oxide, it does not have any cationic groups and it is not a pluronic. Applicants respectfully submit Poly-DL-lactide (PLA) does not fall within the scope of Claim 22.

Additionally, with respect to Claim 36, applicants submit that particle compositions having chitosan distributed throughout the particle are novel over and are not made obvious by the prior art. There is no disclosure in the prior art of microparticles having a chitosan distributed throughout the particle. Illum at page 6, lines 23-24, states that their compositions may be formulated as dry powders or in the form of microparticles. There is no other mention of microparticle formulations, so conventional microparticle technology must be considered. In conventional microparticle technology, such as that described in Eyles, microparticles are formed using a particle forming material, e.g. PLA, and any additional components, such as drugs or adjuvants, are coated onto the surface of those ready formed microparticles. In Eyles, microparticles of PLA are formed and the antigen (Y. Pestis) and the adjuvant (CTB) are coated onto those particles. The antigen and adjuvant are not, therefore, distributed throughout the microparticle. This additional feature of dependent Claim 36 is both new and non-obvious over the prior art of record. Accordingly, applicants respectfully submit they have overcome the Examiner's rejection under 35 U.S.C. §103(a) and request its withdrawal.

In the Final Office Action mailed May 12, 2005, the Examiner rejected Claim 23 under 35 U.S.C. §103(a), as being unpatentable over Illum (WO 97/20576) (discussed above) in view of Eyles (discussed above). Applicants respectfully traverse.

As explained above, Illum and Eyles fail to teach or suggest a polycationic carbohydrate, wherein the polycationic carbohydrate is a water-soluble alkylated chitosan selected from the group consisting of trimethyl chitosan and N-carboxymethyl chitosan or a salt thereof. However, in order to facilitate prosecution applicants have canceled Claim 23. Applicants respectfully submit that the amendments to the claims render the rejection moot. Applicants respectfully submit they have overcome the Examiner's rejection under 35 U.S.C. §103(a) and request its withdrawal.

Claim rejections under 35 U.S.C. §112, first paragraph

In the Final Office Action mailed May 12, 2005, the Examiner rejected Claims 38-39 under 35 U.S.C. §112, first paragraph, for failing to comply with the written description requirement.

In an effort to facilitate prosecution, applicants have canceled Claims 38-39. Applicants respectfully submit that the amendments to the claims render the rejection moot. Applicants respectfully submit they have overcome the Examiner's rejection under 35 U.S.C. §112, first paragraph, and request its withdrawal.

In the Final Office Action mailed May 12, 2005, the Examiner rejected Claims 38-39 under 35 U.S.C. §112, first paragraph, for failing to comply with the written description requirement. The Examiner stated that the claims contain subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention.

In an effort to facilitate prosecution applicants have canceled Claims 38-39. Applicants respectfully submit that the amendments to the claims render the rejection moot. Applicants respectfully submit they have overcome the Examiner's rejection under 35 U.S.C. §112, first paragraph, and request its withdrawal.

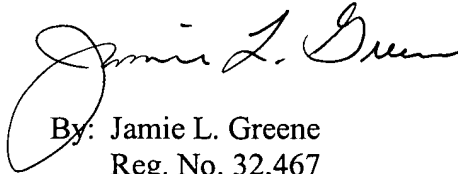
CONCLUSION

Based upon the amendments and remarks provided above, applicants believe that Claims 1, 3-6, 11-22, 36-37 are in condition for allowance. A Notice of Allowance is therefore respectfully solicited.

No additional fees are believed due; however, the Commissioner is hereby authorized to charge any additional fees that may be required, or credit any overpayment, to Deposit Account No. 11-0855.

If the Examiner believes any informalities remain in the application that may be corrected by Examiner's Amendment, or there are any other issues that can be resolved by telephone interview, a telephone call to the undersigned attorney at (404) 815-6500 is respectfully solicited.

Respectfully submitted,


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